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Crystal and molecular structure of anhydroerythromycin *A* cyclic carbonate *N*-methyl iodide

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Abstract

The crystal and molecular structure of $C_{39}H_{66}INO_{13} \cdot CH_3OH$ has been determined by single-crystal x-ray diffraction analysis. The compound crystallizes in the monoclinic space group $P2_1$, with $a = 14.35(1)$, $b = 14.38(1)$, $c = 10.91(1)$ Å, $\beta = 96.10(5)^\circ$, and $Z = 2$. Three-dimensional intensity data were collected on a four-circle fully automated diffractometer. The structure was solved by the heavy-atom method. The positions of all atoms have been refined by block-diagonal and full-matrix least squares, using anisotropic temperature factors. The final R value was 0.109 for 2194 independent reflections. The analysis does not confirm the hypothetical structure proposed by the Eli Lilly group, as far as a position of a cyclic carbonate moiety is concerned. They postulated that the cyclic carbonate moiety was attached to C(9) and C(11) of the erythronolide. The results obtained by us show that the cyclic carbonate moiety is attached to C(11) and C(12). The absolute configuration of the asymmetric centers agrees fully with that established for erythromycin *A*.

Introduction

Macrolide antibiotics of the erythromycin group, produced by *Streptomyces erythreus*, are characterized by the presence in the molecule of a macrolide lactone ring (erythronolide) and two glycosidically bonded sugar moieties (cladinose and desosmine) as their major structural features. The most important member of the erythromycin group is erythromycin *A*, which has found a broad application as a clinical antibiotic, active against gram-positive bacteria including those resistant to other antibiotics.

The complete structures of erythromycin *A*, $C_{37}H_{67}NO_{13}$, and *B*, $C_{37}H_{67}NO_{12}$, were determined in Eli Lilly laboratory (Wiley, et al. 1957*a*; Wiley, et al. 1957*b*). The three-dimensional structure and absolute configuration of erythromycin *A* were elucidated by x-rays in 1965 (Harris et al. 1965).

Erythromycins quite easily undergo a number of intramolecular reactions, leading to the formation of some secondary structures which have to be taken into consideration in the isolation of these antibiotics. Very typical is the formation of a hemiacetal ring structure and other products of dehydration.

The efficacy of erythromycin *A* against bacteria, and its therapeutic properties, has resulted in a great number of semisynthetic derivatives aimed at the development of modified drugs with higher activity, better solubility, and improved property of resorption from the gastrointestinal tract. Erythomycin *A* cyclic carbonate commands attention as a first modification product exhibiting an antimicrobial activity higher than that of erythromycin *A* itself.

Under suitable conditions, erythromycin *A* cyclic carbonate is prepared by reacting erythromycin with ethylene carbonate (Murphy et al. 1968; Bojarska-Dahlig and Sławiński, 1972). The hypothetical structure of the compound postulated by the Eli Lilly group includes an internal 6,9-hemiacetal ring, with the carbonate moiety attached to the C(9) and C(11) carbon atoms of the erythronolide.

Owing to particular activity properties of the above-mentioned compound, elucidation of its complete structure is of interest in regard to the problem of the structure–activity relationship in erythromycin derivatives and is indispensable for studying further reaction products of the carbonate.

We have performed the x-ray analysis of the molecular and crystal structure of the *N*-methyl iodide derivative of erythromycin *A* cyclic carbonate (Hempel et al., 1975). The compound can be easily obtained by treatment of erythromycin *A* carbonate with methyl iodide in an organic solvent. The derivative, with a heavy atom introduced, is stable, crystalline, and suitable for x-ray work. The results of the structure analysis show that the carbonate moiety is on C(11) and C(12). The product appeared to be in 8,9-anhydro form. Our results have been supplemented by NMR and spectrometric studies which indicated that the anhydro form of the

compound is a result of a dehydration process which occurred during the reaction with CH_3I, and that erythromycin carbonate itself exists in equilibrium ketone and hemiacetal structures (Zieliński et al., 1976; Sławiński et al., 1975).

Experimental

The compound was synthesized and kindly supplied by Professor H. Bojarska-Dahlig of the Institute of Pharmaceutical Industry of Warsaw. Crystals suitable for x-ray work were grown from a methanol–ethyl acetate–water mixture in the form of colorless prisms elongated in the *b* direction. The dimensions of the crystal selected for this analysis were 0.4, 1.0, 0.5 mm.

Crystal data

Molecular formula	$C_{39}H_{66}INO_{13} \cdot CH_3OH$
FW	900
M.P.	226–228°C
System	Monoclinic
a	14 · 35(1) Å
b	14 · 38(1)
c	10 · 91(1)
β	96 · 10(5)°
V_c	2241 Å^3
D_m	1 · 36 g cm^{-3}
D_c	1 · 39
Z	2
Space group	$P2_1$
F(000)	964

The space group was determined from precession photographs recorded with Cu $K\alpha$ radiation. The diffraction symmetry indicated space group $P2_1$ or $P2_1/m$. As the unit cell contains two asymmetric molecules, $P2_1$ is the only possibility. Cell dimensions were obtained by a least-squares refinement of 16 high-angle reflections measured on a diffractometer. The observed crystal density was measured by flotation in aqueous potassium iodide. Intensity data collection was performed on a Hilger-Watts four-circle fully automated diffractometer with graphite-monochromated Cu $K\alpha$ radiation. The crystal was so oriented that *b* coincided with the ϕ-axis of the four-circle goniostat.

The integrated intensity measurements were made with a $\theta/2\theta$ scan technique at a rate of 1° per minute over 2θ ranges of 2°. The background was counted for 20 sec at each of the scan limits. During the data collection routine measurements of one standard reflection after every 50 reflections showed that the crystal was stable and properly aligned; the maximum

Table 1. *Final positional and thermal parameters of nonhydrogen atoms (all quantities ×10⁴), with esd's in parentheses; temperature factors* = $\exp[-(h^2B_{11} + k^2B_{22} + l^2B_{33} + hkB_{12} + hlB_{13} + klB_{23})]$

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(01)	6477(24)	1572(23)	7658(24)	79(24)	74(28)	107(35)	60(55)	−124(49)	−25(48)
C(02)	5925(22)	1182(25)	6404(24)	66(20)	56(25)	56(27)	−34(44)	−58(38)	−47(38)
C(03)	4897(19)	0988(22)	6631(23)	41(17)	45(21)	55(25)	49(39)	−29(33)	22(32)
C(04)	4689(19)	−0082(25)	6199(24)	43(17)	70(26)	57(27)	−44(45)	25(35)	−14(36)
C(05)	3767(20)	−0309(19)	6575(24)	62(19)	6(16)	65(28)	−2(36)	−27(36)	28(31)
C(06)	6162(24)	3861(23)	2292(23)	88(26)	70(22)	22(24)	56(41)	−73(40)	−40(38)
C(07)	5509(21)	3045(17)	2516(21)	96(21)	2(12)	58(24)	−12(28)	−56(36)	−9(30)
C(08)	4924(22)	3048(24)	1164(25)	74(22)	53(24)	71(28)	45(42)	−49(41)	−66(40)
C(09)	4972(23)	3786(26)	0732(27)	69(23)	59(26)	77(32)	−29(49)	−1(43)	14(42)
C(10)	4665(18)	4141(16)	9374(20)	66(17)	17(13)	23(21)	49(25)	−62(31)	20(29)
C(11)	5909(16)	0060(19)	0487(18)	40(14)	22(17)	35(19)	−13(27)	1(26)	5(31)
C(12)	6875(21)	0019(27)	0266(23)	65(19)	95(31)	35(24)	−43(46)	−80(37)	61(42)
C(13)	7167(15)	0942(17)	9574(19)	35(13)	30(16)	34(20)	−32(25)	−24(25)	−17(29)
C(14)	8180(19)	1095(26)	9492(24)	30(16)	91(30)	58(27)	−41(48)	−43(35)	23(36)
C(15)	8618(21)	0759(25)	8586(26)	58(20)	69(26)	71(30)	11(46)	13(40)	56(41)
C(16)	5978(19)	1990(20)	5435(21)	70(19)	33(17)	43(22)	−27(31)	23(33)	80(33)
C(17)	4724(17)	−0099(20)	4758(23)	56(19)	36(18)	59(28)	3(30)	5(34)	−15(36)
C(18)	7041(19)	3652(25)	1856(26)	29(16)	105(24)	90(32)	41(33)	37(37)	−26(46)
C(19)	4309(22)	2202(23)	0893(26)	85(22)	50(30)	95(32)	−5(45)	−43(44)	16(39)
C(20)	5331(18)	4286(19)	8650(21)	52(16)	42(17)	50(24)	31(27)	76(32)	−6(34)
C(21)	2770(22)	4101(26)	0321(28)	58(20)	66(26)	102(32)	−63(45)	−89(41)	−9(41)
C(22)	6918(22)	0353(23)	2142(27)	74(22)	32(20)	89(32)	−10(44)	−36(43)	7(37)
O(23)	7100(16)	0613(15)	3282(19)	121(18)	64(13)	83(22)	−33(27)	−28(32)	13(30)
O(24)	5984(15)	0463(18)	1764(18)	84(16)	69(18)	75(20)	13(32)	−53(29)	13(30)
O(25)	7482(13)	0092(14)	1439(16)	59(12)	43(13)	82(18)	−5(22)	−23(24)	−2(27)
O(26)	6632(14)	0766(17)	8350(18)	71(14)	70(17)	91(21)	−51(31)	−102(29)	49(28)

O(27)	6692(13)	2314(15)	7908(16)	76(26)	26(14)	111(19)	18(30)	−69(26)	−1(26)
O(28)	5606(13)	4481(19)	1307(16)	58(13)	102(20)	57(18)	−3(32)	−77(25)	−6(27)
O(29)	4205(14)	1553(17)	6013(16)	57(13)	66(17)	76(20)	−45(31)	−36(26)	−49(27)
O(30)	3467(12)	2216 (13)	7584(15)	55(11)	29(15)	91(20)	8(26)	−15(24)	−19(21)
O(31)	1053(11)	2695(17)	6171(19)	29(10)	80(16)	176(26)	−6(22)	−3(25)	12(36)
O(32)	2402(12)	2132(17)	4607(17)	41(11)	108(24)	104(21)	10(33)	−25(25)	43(24)
O(33)	6802(10)	4130(12)	4415(14)	30(09)	34(10)	59(16)	27(16)	−32(19)	42(21)
O(34)	8268(12)	4554(16)	4060(16)	33(11)	61(15)	72(19)	7(30)	−35(23)	65(23)
O(35)	7240(13)	4199(17)	6963(16)	40(11)	87(19)	67(19)	18(32)	−12(23)	29(26)
C(36)	7880(19)	4079(25)	6169(24)	40(17)	83(27)	54(26)	−17(47)	−93(35)	67(39)
C(37)	8866(17)	4668(24)	6623(23)	31(15)	59(23)	66(26)	−23(42)	−45(32)	49(33)
C(38)	9573(16)	4566(20)	5719(23)	28(14)	55(19)	71(23)	−2(27)	6(31)	64(39)
C(39)	0904(16)	0052(22)	5493(24)	21(13)	45(21)	101(28)	6(28)	16(31)	−60(43)
C(40)	7587(17)	4669(21)	4913(22)	27(15)	35(19)	55(25)	−41(38)	−18(31)	44(30)
C(41)	8697(21)	4463(28)	9026(26)	68(20)	126(29)	59(22)	−2(41)	−29(39)	−94(50)
C(42)	9288(21)	3195(24)	7783(24)	62(20)	70(24)	50(27)	−82(45)	−46(37)	62(39)
C(43)	0271(18)	4467(26)	8189(27)	27(16)	97(26)	105(33)	−13(35)	−91(37)	18(49)
C(44)	4036(16)	2385(14)	6702(20)	60(15)	1(09)	82(23)	−3(23)	25(30)	33(29)
C(45)	3607(19)	3145(16)	5728(28)	57(17)	8(12)	150(38)	41(25)	−102(41)	−10(35)
C(46)	2535(18)	2966(24)	5327(26)	23(14)	75(27)	90(30)	21(46)	−44(35)	−38(31)
C(47)	2079(21)	2866(23)	6457(28)	57(19)	60(26)	117(34)	9(46)	−34(42)	−54(35)
C(48)	2450(18)	1971(23)	7228(23)	36(16)	68(22)	71(26)	0(31)	−4(33)	−38(40)
C(49)	1993(25)	1779(23)	8410(29)	94(25)	61(22)	113(36)	−3(38)	91(49)	−26(45)
C(50)	2206(24)	3796(24)	4532(29)	84(23)	36(21)	111(34)	−12(46)	−16(45)	−38(39)
C(51)	2825(19)	2047(24)	3452(26)	49(18)	73(29)	77(29)	−78(45)	−2(37)	22(36)
C(52)	0256(19)	0015(25)	6453(27)	39(17)	53(25)	111(33)	−16(48)	5(37)	−18(35)
N(53)	9280(16)	4168(16)	7953(21)	67(15)	23(13)	98(26)	−33(24)	−78(32)	51(32)
I(54)	0493(01)	2500(00)	1162(02)	78(01)	121(02)	107(02)	−20(04)	−44(02)	28(04)
C(55)	8987(35)	2026(36)	4146(48)	114(38)	93(45)	311(76)	84(65)	−162(88)	−121(94)
O(56)	0036(17)	2010(19)	4035(22)	81(16)	113(20)	163(30)	−11(30	−6(35)	56(40)

intensity variation was 0.9% from its mean value. A total of 2388 independent reflections with $(\sin\theta)/\lambda < 0.5$ was measured. Of these, 194 had a net intensity less than $3\sigma(I)$, where $\sigma(I)$ is given by $[N + k^2(N_{B1} + N_{B2})]^{1/2}$. In this expression, N is the total number of counts accumulated during the scan, N_{B1} and N_{B2} are the background counts at either end of the scan range and k is the ratio of the total scan time to the total background scan time. The intensities were corrected for Lorentz and polarization effects but not for absorption. The reduction to structure amplitudes was performed during the data collection using the Hilger-Watts Software System.

Structure determination and refinement

The structure analysis, which presented some difficulty, was based on the heavy-atom method. The position of the iodine atom was derived from the Harker section $P(u,\frac{1}{2},w)$ of the Patterson map.

The coordinates of the iodine atom were consistent with those obtained by us earlier from two-dimensional ($h0l$) photographic data. Unrefined coordinates for the iodine atom were $x = 0.049$, $y = \frac{1}{4}$, $z = 0.116$.

The atomic scattering factors used for C,N,O, and I were taken from the *International Tables for X-ray Crystallography* (1969). An initial R-value ($R = \Sigma||F_o| - |F_c||\Sigma|F_o|$) at this point was 0.41. A three-dimensional Fourier synthesis based on the phases of the iodine atom was calculated. From the map, positional parameters of 21 peaks were derived, treated as carbon atoms, to give a new set of phases (R increased to 0.45). After three subsequent Fourier syntheses, 56 atoms of the molecule were localized giving an R value of 0.23. Bond scan calculations made at this stage showed that in the trial model atoms of both possible enantiomeric structures were present. In space group $P2_1$ a monatomic structure is always a priori centrosymmetric, taking into consideration its symmetry equivalent. Hence, the first electron density map, based only on the iodine atom, showed a pseudomirror-symmetry. From the bond scan results, a 10-atoms fragment, which made good chemical sense, was chosen (the R factor at this stage was 0.37). Next, an electron density calculation was performed and 44 atoms were readily identified ($R = 0.24$). Another Fourier synthesis was calculated and all 54 nonhydrogen atoms in the molecule were found.

Minimizing the quantity $\Sigma[(F_o) - (F_c)]^2$, all fractional coordinates of the 54 atoms were refined by three cycles of block-diagonal least squares, using isotropic temperature factors to give $R = 0.18$. A three-dimensional difference Fourier synthesis was carried out and a methanol molecule was detected. Two more cycles of block-diagonal least squares isotropic refinement on the parameters of 56 atoms were applied and the residual decreased to 0.16. At this stage three cycles of block-diagonal anisotropic refinement were carried out, using only those reflections in least squares summation for

which $|F_c|$ was 75% of $|F_o|$; 1529 such reflections were included (residual = 0.07). In the last step of the refinement procedures, two cycles of full-matrix anisotropic least squares were performed over 25 atoms in the asymmetric unit that exhibited the most prominent shifts in positional parameters (all atoms were included). The full set of 2194 reflections was used, and the final R value obtained was 0.109. The final fractional coordinates and anisotropic thermal parameters are presented in Table 1. No attempt was made to locate the hydrogen atoms. All calculations were carried out with the NRC crystallographic computer programs (Ahmed et al., 1968). The programs were kindly supplied by Dr. Lesley S. Dent-Glasser from the Department of Chemistry, University of Aberdeen, and adapted to an ICL4/50 computer by Mr J. S. Knowles of the Department of Computing, University of Aberdeen, Scotland.

Description and discussion of the structure

Molecular structure

The atoms of the organic molecule are numbered and presented in Fig. 1. The *b*-axis projection of the molecule is shown in Fig. 2. Bond lengths and angles are gathered in Tables (2) and (3) respectively.

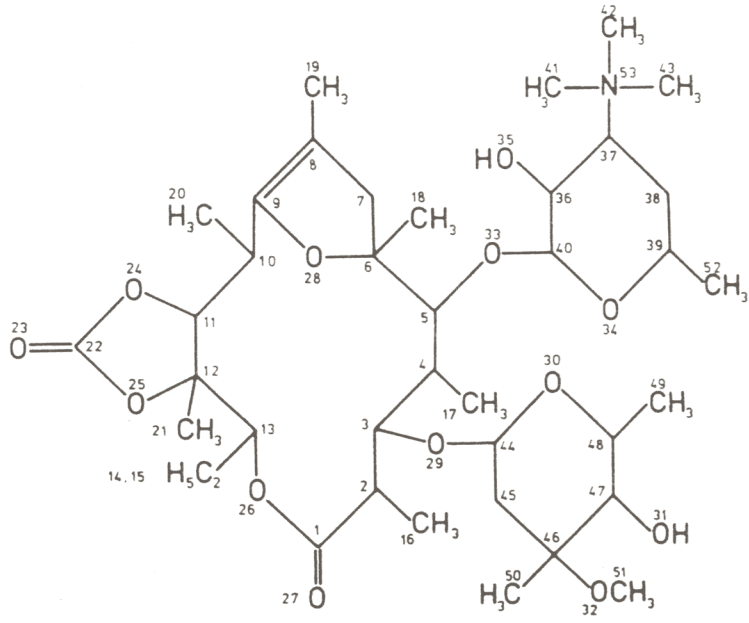

Fig. 1. Atom numbering.

Table 2. *Bond distances (Å) with esd's in parentheses*

C(1)–C(2)	1.60(4)	C(1)–O(26)	1.38(4)	C(1)–O(27)	1.13(4)
C(2)–C(3)	1.55(4)	C(2)–C(16)	1.58(4)	C(3)–C(4)	1.63(5)
C(3)–O(29)	1.40(3)	C(4)–C(5)	1.46(4)	C(4)–C(17)	1.58(4)
C(5)–C(6)	1.71(4)	C(5)–O(33)	1.52(3)	C(6)–C(7)	1.54(4)
C(6)–C(18)	1.43(4)	C(6)–O(28)	1.55(4)	C(7)–C(8)	1.62(4)
C(8)–C(9)	1.17(5)	C(8)–C(19)	1.51(5)	C(9)–C(10)	1.58(4)
C(9)–O(28)	1.45(4)	C(10)–C(11)	1.57(3)	C(10)–C(20)	1.56(3)
C(11)–C(12)	1.43(4)	C(11)–O(24)	1.50(3)	C(12)–C(13)	1.61(4)
C(12)–C(21)	1.57(5)	C(13)–C(14)	1.48(4)	C(12)–O(25)	1.47(3)
C(14)–C(15)	1.32(4)	C(13)–O(26)	1.49(3)	C(22)–O(23)	1.30(4)
C(22)–O(24)	1.37(4)	C(22)–O(25)	1.23(3)	O(29)–C(44)	1.45(3)
O(30)–C(44)	1.35(3)	O(30)–C(48)	1.51(3)	O(31)–C(47)	1.49(3)
O(32)–C(46)	1.44(4)	O(32)–C(51)	1.46(3)	O(33)–C(40)	1.43(3)
O(34)–C(39)	1.43(3)	O(34)–C(40)	1.43(3)	O(35)–C(36)	1.34(3)
C(36)–C(37)	1.68(4)	C(36)–C(40)	1.63(4)	C(37)–C(38)	1.50(3)
C(37)–N(53)	1.67(3)	C(38)–C(39)	1.58(4)	C(39)–C(52)	1.47(4)
C(41)–N(53)	1.57(4)	C(42)–N(53)	1.41(4)	C(43)–N(53)	1.48(4)
C(44)–C(45)	1.60(3)	C(45)–C(46)	1.57(4)	C(46)–C(47)	1.46(4)
C(46)–C(50)	1.52(5)	C(47)–C(48)	1.60(4)	C(48)–C(49)	1.53(4)
C(55)–O(56)	1.52(6)				

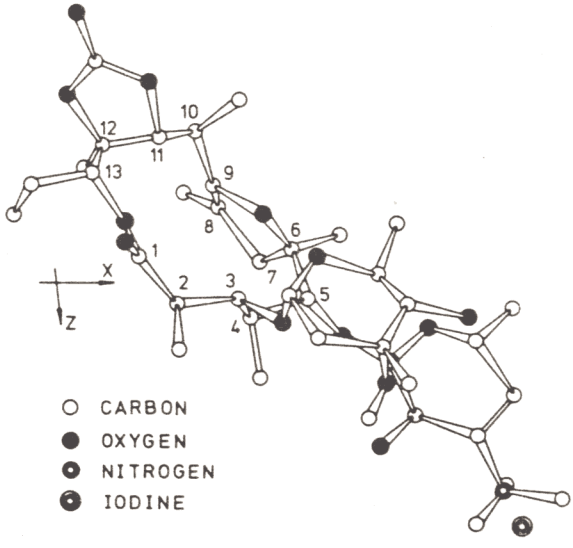

Fig. 2. Projection of the molecule along *b*.

Table 3. *Bond angles (deg), with esd's in parentheses*

O(26)–C(1)–C(2)	102(2)	O(27)–C(1)–C(2)	128(3)
C(3)–C(2)–C(1)	108(2)	C(16)–C(2)–C(1)	105(2)
O(27)–C(1)–O(26)	129(3)	C(13)–O(26)–C(1)	112(2)
C(16)–C(2)–C(3)	110(2)	C(4)–C(3)–C(2)	106(2)
O(29)–C(3)–C(2)	117(2)	O(29)–C(3)–C(4)	108(2)
C(5)–C(4)–C(3)	106(2)	C(17)–C(4)–C(3)	106(2)
C(44)–O(29)–C(3)	112(2)	C(17)–C(4)–C(5)	113(2)
C(6)–C(5)–C(4)	112(2)	O(33)–C(5)–C(4)	110(2)
O(33)–C(5)–C(6)	97(2)	C(7)–C(6)–C(5)	114(2)
C(18)–C(6)–C(5)	113(2)	O(28)–C(6)–C(5)	95(2)
C(40)–O(33)–C(5)	108(2)	C(18)–C(6)–C(7)	118(2)
O(28)–C(6)–C(7)	106(2)	C(8)–C(7)–C(6)	97(2)
O(28)–C(6)–C(18)	107(2)	C(9)–O(28)–C(6)	99(2)
C(9)–C(8)–C(7)	108(3)	C(19)–C(8)–C(7)	114(2)
C(19)–C(8)–C(9)	135(3)	C(10)–C(9)–C(8)	130(3)
O(28)–C(9)–C(8)	121(3)	O(28)–C(9)–C(10)	106(2)
C(11)–C(10)–C(9)	106(2)	C(20)–C(10)–C(9)	111(2)
C(20)–C(10)–C(11)	113(2)	C(12)–C(11)–C(10)	120(2)
O(24)–C(11)–C(10)	103(2)	O(24)–C(11)–C(12)	101(2)
C(13)–C(12)–C(11)	110(2)	C(21)–C(12)–C(11)	118(2)
O(25)–C(12)–C(11)	110(2)	C(22)–O(25)–C(12)	102(2)
C(21)–C(12)–C(13)	113(2)	O(25)–C(12)–C(13)	100(2)
C(14)–C(13)–C(12)	117(2)	O(26)–C(13)–C(12)	98(2)
O(25)–C(12)–C(21)	103(2)	C(22)–O(25)–C(12)	101(2)
O(26)–C(13)–C(14)	113(2)	C(15)–C(14)–C(13)	122(3)
O(24)–C(22)–O(23)	110(3)	O(25)–C(22)–O(23)	127(3)
O(25)–C(22)–O(24)	122(3)	O(30)–C(44)–O(29)	112(2)
C(45)–C(44)–O(29)	107(2)	C(48)–O(30)–C(44)	119(2)
C(45)–C(44)–O(30)	112(2)	C(47)–C(48)–O(30)	102(2)
C(49)–C(48)–O(30)	108(2)	C(46)–C(47)–O(31)	111(2)
C(48)–C(47)–O(31)	104(2)	C(51)–O(32)–C(46)	120(2)
C(45)–C(46)–O(32)	111(2)	C(47)–C(46)–O(32)	109(2)
C(50)–C(46)–O(32)	109(2)	O(34)–C(40)–O(33)	104(2)
C(36)–C(40)–O(33)	98(2)	C(40)–O(34)–C(39)	108(2)
C(38)–C(39)–O(34)	109(2)	C(52)–C(39)–O(34)	108(2)
C(36)–C(40)–O(34)	110(2)	C(37)–C(36)–O(35)	111(2)
C(40)–C(36)–O(35)	110(2)	C(40)–C(36)–C(37)	97(2)
C(38)–C(37)–C(36)	111(2)	N(53)–C(37)–C(36)	104(2)
N(53)–C(37)–C(38)	109(2)	C(39)–C(38)–C(37)	104(2)
C(41)–N(53)–C(37)	111(2)	C(42)–N(53)–C(37)	109(2)
C(43)–N(53)–C(37)	106(2)	C(52)–C(39)–C(38)	109(2)
C(42)–N(53)–C(41)	112(2)	C(43)–N(53)–C(42)	107(2)
C(46)–C(45)–C(44)	111(2)	C(47)–C(46)–C(45)	107(2)
C(50)–C(46)–C(45)	105(2)	C(50)–C(46)–C(47)	115(2)
C(48)–C(47)–C(46)	112(2)	C(49)–C(48)–C(47)	116(2)

Table 4. *Least-squares planes and atomic deviations* (Å): *all equations are expressed in orthogonal Ångstrom space*

Plane 1	$0.133X + 0.952Y - 0.276Z = 1.998$	
	C(11) −0.0972	
	C(12) 0.0998	
	C(22) −0.0243	
	O(23) 0.0070	
	O(24) 0.0675	
	O(25) 0.0529	
	Sigma (delta squared) = 0.0274	
Plane 2	$0.914X - 0.138Y - 0.380Z = -4.217$	
	C(1) −0.0033	
	C(2) 0.0010	
	O(26) 0.0010	
	O(27) 0.0014	
	Sigma (delta squared) = 0.0000	
Plane 3	$0.827X + 0.400Y - 0.395Z = -0.419$	
	C(7) −0.0429	
	C(8) −0.0570	
	C(9) 0.0835	
	C(10) −0.0606	
	C(19) 0.0442	
	O(28) 0.0329	
	Sigma (delta squared) = 0.0188	
Plane 4	$0.737X + 0.416Y - 0.533Z = 1.558$	
	C(6) −0.1820	
	C(7) 0.1698	
	C(8) −0.1075	
	C(9) −0.0038	
	O(28) 0.1234	
	Sigma (delta squared) = 0.0888	
Plane 5	$0.309X - 0.813Y - 0.494Z = 5.375$	
	C(45) 0.0191	
	C(46) −0.0185	
	C(48) 0.0193	
	O(30) −0.0199	
	C(44)[a]	
	C(47)[a]	
	Sigma (delta squared) = 0.0015	
Plane 6	$0.546X + 0.835Y - 0.061Z = -0.055$	
	C(36) 0.0033	
	C(37) −0.0034	
	C(39) 0.0040	
	O(34) −0.0039	(desosamine)
	C(40)[a]	
	C(38)[a]	
	Sigma (delta squared) = 0.0001	

Table 4.—*cont.*

Matrix for the transformation to orthogonal Å coordinates

$T(1,1)$ =	14.35600
$T(1,2)$ =	0.00000
$T(1,3)$ =	−1.15987
$T(2,1)$ =	0.00000
$T(2,2)$ =	14.38600
$T(2,3)$ =	0.00000
$T(3,1)$ =	0.00000
$T(3,2)$ =	0.00000
$T(3,3)$ =	10.85320

[a] Atom not included in plane calculation.

Table 5. *Dihedral angles (deg) in the sugar moieties and double-bond neighborhood*

C(40)–O(34)–C(39)–C(38)	68(1)
C(40)–C(36)–C(37)–C(38)	63(1)
C(44)–O(30)–C(48)–C(47)	59(1)
C(44)–C(45)–C(46)–C(47)	51(1)
C(7)–C(8)–C(9)–C(10)	170(0.5)
C(7)–C(8)–C(9)–O(28)	9(0.5)
C(19)–C(8)–C(9)–C(10)	25(0.5)
C(19)–C(8)–C(9)–O(28)	174(0.5)

Considering that no absorption correction was applied, the intramolecular bond lengths and angles are sufficiently in agreement with accepted values (*International Tables for X-ray Crystallography, 1969*). The double-bond distance(1.16 Å) between C(8) and C(9) is shorter than the usual (1.337 Å).

Knowing the absolute configuration of sugar components (Hofheinz et al., 1962; Lemal et al., 1962; Woo et al., 1962; Richardson, 1963) and erythronolide (Harris et al. 1965), we were able to define the configuration of the asymmetric centers of the compound at hand. It is fully consistent with that previously established for erythromycin *A* itself, except that in our structure there is no asymmetric center at the C(8) erythronolide carbon atom, and at C(12) the configuration is *R*. The configuration at C(12) arises from the change of substituents on this carbon atom.

Figure 2 shows clearly the α-glycosidic linkage of cladinose and the β-linkage of desosamine moieties. Both sugars have a *chair* conformation $^1C_4$ for cladinose and $^4C_1$ for desosamine (Schwarz, 1973).

The average C–O bond distance in both cladinose and desosamine is (1.43 Å). It agrees fairly well with the accepted value. The average C–C bond distance in cladinose is (1.59) and in desosamine (1.55 Å).

Least-squares planes through various groups of atoms and dihedral angles are shown in Tables 4 and 5, respectively. The planarity of the group of

atoms C(45), C(46), C(48), O(30) of cladinose and C(36), C(37), C(39), O(34) of desosamine is quite good, especially the latter. The group of atoms C(1), C(2), O(26), O(27) of the erythronolide should be planar, and small deviations from planarity may be neglected. The group C(7), C(8), C(9), C(19), C(10), O(28), being a part of both the 5-membered hemiacetal ring and the macrolide ring, has a visible nonplanarity (strained structure).

Crystal structure and interatomic contacts

The arrangement of the molecules in the unit cell in presented in Fig. 3. The dimensions of the hydrogen bonds are summarized in Table 6.

In the crystal structure, the only evident intermolecular hydrogen bond that spans organic molecules exists between the hydrogen atom on O(35)

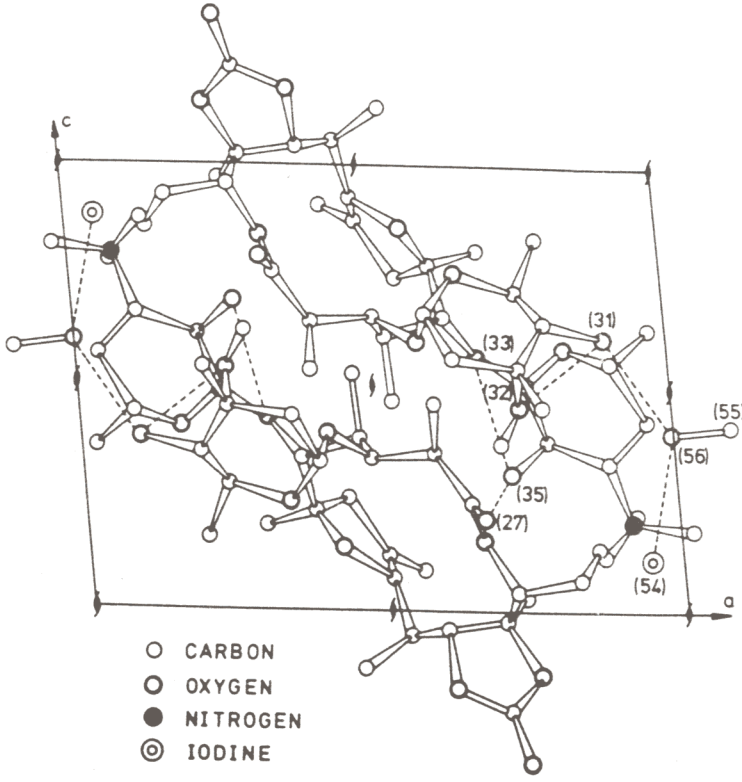

Fig. 3. Packing of molecules in the unit cell, viewed down *b*, showing the hydrogen-bond system.

Table 6. *Intramolecular and intermolecular hydrogen-bond distances* (Å)

O(31)–O(32)	2.83
O(56)–O(31)	2.80
O(35)–O(33)	2.79
O(56)–I(54)	3.35
O(35)–O(27)	3.03

oxygen atom of a first molecule and O(27) oxygen of a second; it is a bifurcated hydrogen bond. From the distance between the two oxygen atoms (3.035 Å), one can judge that the hydrogen bond is not strong. The units connected by the hydrogen bond in question form an infinite chain parallel to *b*. Between the infinite chains of hydrogen-bonded molecules there are no other intermolecular distances appreciably shorter than the sum of appropriate van der Waals radii; thus, they are linked by van der Waals forces, rather than by hydrogen bonds, and are related by a diad screw axis. Short intermolecular contacts are listed in Table 7.

Table 7. *The shortest intermolecular contact distances* (Å)

$O(35^{I})$	$\cdots C(20^{II})$	3.22
$O(25^{III})$	$\cdots C(43^{I})$	3.33
$O(23^{III})$	$\cdots C(55^{I})$	3.44
$O(31^{I})$	$\ldots C(38^{IV})$	3.43
$O(31^{I})$	$\cdots C(42^{IV})$	3.31

Superscripts indicate the following equivalent positions:

I	X	Y	Z
II	X	Y	$Z+1$
III	$X+1$	Y	$Z+1$
IV	$2-X$	$Y+1/2$	$1-Z$

In the molecule itself, there are two intramolecular hydrogen bonds forming 5-membered rings. The first is between the oxygen atoms O(35) and O(33) of the desosamine moiety, and the second between the oxygen atoms O(31) and O(32) of the cladinose. From a geometrical point of view, a hydrogen bond is said to exist if a hydrogen atom–heavy atom distance is 0.2 Å or more shorter than the sum of van der Waals radii. In the absence of hydrogen atoms, one cannot treat any remaining interatomic interactions

Table 8. *Distances (Å) between nonbonded atoms of one molecule*

C(2)	···	C(17)	2.99
C(3)	···	O(26)	2.97
C(3)	···	O(30)	2.98
C(4)	···	O(28)	2.87
C(5)	···	O(29)	2.83
C(7)	···	O(33)	3.06
C(11)	···	O(26)	2.84
C(11)	···	O(28)	2.89
C(13)	···	O(27)	2.72
C(14)	···	O(25)	2.84
C(15)	···	O(26)	2.83
C(16)	···	O(27)	2.82
C(16)	···	O(29)	2.76
C(17)	···	O(29)	2.88
C(17)	···	O(35)	2.69
C(18)	···	O(33)	2.93
C(18)	···	O(34)	3.11
C(20)	···	O(24)	2.75
C(20)	···	O(28)	2.90
C(21)	···	C(10)	3.01
C(21)	···	O(26)	2.88
O(29)	···	O(32)	2.98
O(30)	···	C(46)	2.88
O(31)	···	C(49)	2.97
O(32)	···	C(48)	2.86
O(34)	···	C(37)	2.84
O(35)	···	C(41)	2.93
O(53)	···	N(53)	3.01
C(36)	···	C(42)	2.84
C(38)	···	C(43)	2.78
C(44)	···	C(47)	2.88
C(50)	···	C(51)	2.88

otherwise than nonbonded. Some interactions are much shorter than the sum of the appropriate van der Waals radii (overcrowded molecular structure): the distances between such atoms of one molecule are listed in Table 8 to illustrate this problem.

A hydrogen atom at O(56) of the methanol molecule is probably involved into two hydrogen bonds: the first with the oxygen atom O(31), and the second with the iodine I(54). It is possible, however, that the hydrogen at O(31) is the one which produces a bifurcated hydrogen bond with O(32) and O(56) oxygen atoms.

Owing to a steric hindrance produced by three methyl groups around the quaternary, positively charged nitrogen atom N(53), the distance between this atom and the iodine atom is (4.897 Å). In the crystal structure of

erythromycin *A* hydroiodide (Harris et al. 1965), when there are only two methyl groups around the nitrogen atom of the desosamine moiety, the distance between N^+ and I^- is 3.52 Å. This short distance seems to be a result of a hydrogen bond of the type N–H · · I, as well as an $N^+ - \cdot \cdot - I^-$ ionic interaction. Such interaction is not possible in our structure because of the methyl groups.

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